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The narrow-sense and common single nucleotide polymorphism heritability of early repolarization☆

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ABSTRACT

Background: Early repolarization (ER) is a risk marker for sudden cardiac death. Higher risk is associated with horizontal/descending ST-segment ER in the inferior or inferolateral ECG leads. Studies in family cohorts have demonstrated substantial heritability for the ER pattern, but genome-wide association studies (GWAS) have failed to identify statistically significant and replicable genetic signals.
Methods and results: We assessed the narrow-sense and common single nucleotide polymorphism (SNP) heritability of ER and ER subtypes using ECG data from 5829 individuals (TwinsUK, BRIGHT and GRAPHIC cohorts). ER prevalence was 8.3%. In 455 monozygous vs 808 dizygous twin pairs, concordances and twin correlations for ER subtypes (except horizontal/descending ST-segment ER) were higher and familial resemblance (except notched ER) was significant. Narrow-sense heritability estimates derived from 1263 female twin pairs using the structural equation program Mx ranged from 0.00–0.47 and common SNP heritability estimates derived from 4009 unrelated individuals of both sexes using Genome-wide Restricted Maximum Likelihood (GREML) ranged from 0.00–0.36, but none were statistically significant.
Conclusion: From our data, ER shows limited genetic predisposition. There appears to be significant environmental influence and these modest narrow-sense and common SNP heritability estimates may explain why previous GWAS have been unsuccessful.

1. Introduction

Early repolarization (ER), particularly in the inferior and inferolateral electrocardiogram (ECG) leads, has emerged as a risk marker for sudden cardiac death (SCD) [1,2]. The morphology of the ST-segment appears important in determining risk for arrhythmic events in the general population and survivors of idiopathic ventricular fibrillation (IVF) [3,4]. ER with a rapidly ascending ST-segment, consistent with historical descriptions of benign ER, is more prevalent in young, male, athletic individuals of Afro-Caribbean ethnicity [5]. It does not appear to confer risk of arrhythmic events, whereas ER with a horizontal/descending ST-segment does [3,4,6].

Pedigree analysis of the families of SCD victims has suggested that ER has autosomal dominant inheritance with incomplete penetrance [7]. Heritability studies conducted in family and community based cohorts

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have demonstrated substantial heritabilities of 50–80% for the ER pattern and its associated morphologies [8,9]. At present, there are little data on the genetic basis of ER. Candidate gene studies have identified a limited number of rare variants in early repolarization syndrome probands, including a gain of function variant in *KCNJ8*, and presumed loss of function variants in *CACNA1C*, *CACNB2*, *CACNA2D1* and *SCN5A* [10–12].

Although previous cohort studies have demonstrated substantial heritability for the ER pattern, genome-wide association studies (GWAS) have been unable to identify a statistically significant and replicable signal [13]. We sought to estimate the heritability of ER, with attention to ST-segment morphology, using twin analyses to determine narrow-sense heritability (the proportion of variance of a trait that is due to additive genetic factors). We then undertook common single nucleotide polymorphism (SNP) based heritability analyses using data from three large independent cohorts. This study therefore adds to prior literature by using both methods to measure heritability.

2. Methods

2.1. Populations

Study subjects were identified from the TwinsUK registry, the MRC British Genetics of Hypertension (BRIGHT) study, and the Genetic Regulation of Arterial Pressure of Humans in the Community (GRAPHIC) study. The TwinsUK cohort is a national register of monozygous (MZ) and dizygous (DZ) adult Caucasian twins recruited as volunteers through a series of media campaigns and not selected for particular diseases or traits [14]. The BRIGHT study comprises over 2000 unrelated hypertensive cases and normotensive controls of white European ancestry recruited in the UK. Case ascertainment and phenotyping has been described previously [15]. Only hypertensive cases had an ECG and these individuals were included in this study regardless of the presence or absence of left ventricular hypertrophy (LVH). The GRAPHIC Study comprises 2024 individuals from 520 nuclear families recruited from the UK general population to investigate the genetic determinants of blood pressure and related cardiovascular traits. The studies have previously been given ethical approval and comply with the Declaration of Helsinki.

Subject age was defined at the time of the ECG. Individuals across all three cohorts with ECG data available were potential candidates for study inclusion. The study exclusion criteria were atrial fibrillation; complete heart block; right or left branch bundle block; a pacemaker; prior history of cardiac arrhythmia, Brugada syndrome, long or short QT syndromes; medical therapy with anti-arrhythmic drugs; or missing data on covariates.

Following exclusion criteria, 5829 individuals had ECG data available for analysis. There were 3539 individuals from TwinsUK (504 MZ and 822 DZ twin pairs, 11 twin pairs with unknown zygosity, 35 twin-sib pairs, 163 other sibs, and 632 singletons), 1358 hypertensive cases from BRIGHT and 932 unrelated individuals from GRAPHIC.

2.2. Electrocardiogram analysis and early repolarization scoring

When more than one ECG was available (TwinsUK), the earliest was used, as prevalence of ER appears to decline with age [1]. TwinsUK and BRIGHT ECGs were evaluated at St George's University of London. Each ECG was examined by two blinded individuals yielding 98% concordance. GRAPHIC ECGs were evaluated in Germany as previously described [9]. To determine interobserver variability between UK and German teams, a subset of 411 ECGs were read in both centres yielding 96% concordance. Differences in opinion were adjudicated by a trained cardiologist.

ER was defined as J-point elevation ≥0.1 mV above the isoelectric line (T-P interval) in ≥2 consecutive leads. ER was described by type: slurred (smooth transition from the QRS to the ST-segment with demonstrable change in gradient), notched (a positive deflection inscribed on the S wave) or mixed (equal prevalence of each type on the same ECG); and territory: inferior (leads II, III, aVF), lateral (leads I, aVL, V4-V6) or inferolateral (2 leads from one territory and ≥1 lead from the other territory) (Fig. 1). The ST-segment morphology was recorded as rapidly ascending (>0.1 mV ST-segment elevation within 100 ms after the J-point or persisting through the ST-segment) or horizontal/descending (≤0.1 mV ST-segment elevation within 100 ms after the J-point) (Fig. 1). Consistent with other studies anterior leads V_1–V_3 were excluded from analysis [1–3]. Heart rate, PR and QT intervals, QRS duration and axis were derived from automated measurements. The QT interval was corrected for heart rate using Bazett's Formula. Sokolow-Lyon criteria were used to determine ECG voltage criteria for LVH.

2.3. Genotyping and imputation

Subjects from the TwinsUK cohort were genome-wide genotyped using the Infinium assay (Illumina, San Diego, USA) across four fully compatible single nucleotide polymorphism (SNP) arrays. The genotyping and quality control of these data have been described elsewhere [16]. Subjects from the BRIGHT study were genotyped with the GeneChip Human Mapping 500 K Array Set (Affymetrix). Only individuals and SNPs passing thresholds for quality control were included in the analysis. Details have been described previously [17]. Subjects from the GRAPHIC study were genotyped using the Illumina HumanOmniExpress-12v1_H 700k platform (Illumina, San Diego, USA).

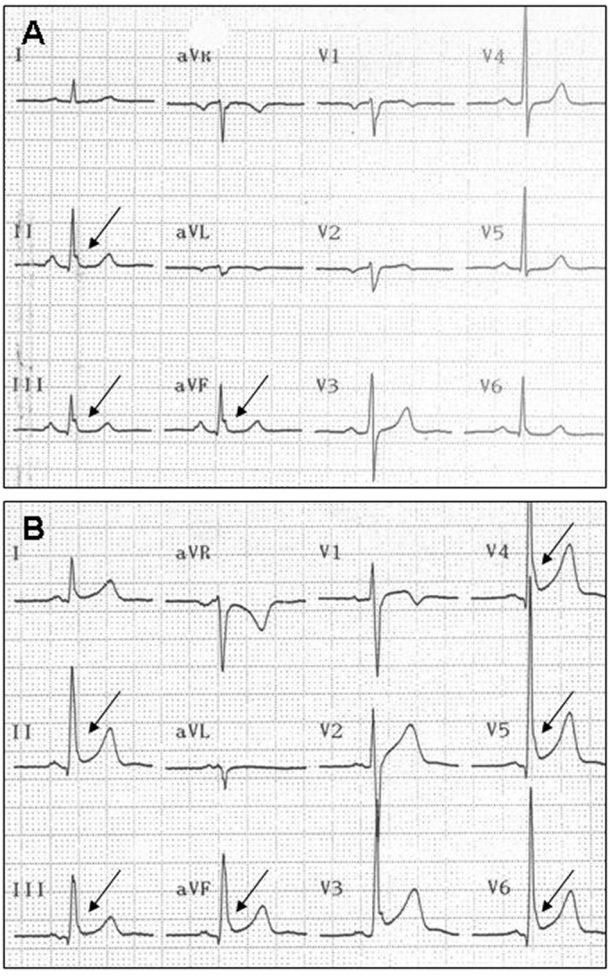

Fig. 1. Examples of early repolarization (ER). Panel A demonstrates notched inferior ER with horizontal/descending ST-segment morphology. Panel B demonstrates slurred inferolateral ER with rapidly ascending ST-segment.

Because the cohorts used different genotyping platforms, the genotype data set of each cohort was enlarged by imputation using the HapMap Phase 3 CEU set as a reference panel [18]. This reference set was chosen as it contains ~1.5×10^6 independent SNPs and the imputed data sets can be used in GREML directly, without further pruning or clumping of SNPs. After imputation, data from the three cohorts were filtered on minor allele frequency >5% and imputation quality >0.5, converted to best-guess genotypes, where only genotypes with a probability of >0.9 were considered valid, and finally filtered on call rate >95%. These high-quality datasets were subsequently merged based on rs-id and filtered on SNPs that were present in all three cohorts. Finally, SNPs that differed significantly in allele frequencies between either pair of cohorts ($p < 0.0001$) were excluded. The resulting data set for heritability estimation contained 532,301 SNPs.

2.4. Heritability estimation

Classical twin modeling was undertaken in the TwinsUK cohort using the DZ and MZ female twin pairs. The narrow-sense heritability of ER and ER subtypes was estimated using the structural equation program Mx (version 1.3.65), meaning that only additive genetic effects were considered [19]. It is possible to quantify the genetic and environmental contribution to a dichotomous variable, such as the presence or absence of ER, by assuming that there is a continuous normally distributed underlying liability to disease and that a threshold of liability divides subjects into two categories: affected and unaffected [20]. MZ and DZ twin pair correlations of the underlying liability distribution were based on 2×2 contingency tables in which the cells contain the frequencies of pairs concordant and discordant for the presence or absence of disease in the MZ and DZ twins. In the classical ACE twin model the differences between MZ and DZ correlations were used to investigate the relative contribution of genetic and environmental influences to individual differences in a trait. The variance of the trait was split into independent components for additive genetic effects (A), common environmental factors (shared by twins within a twin pair) (C) and for unique environmental factors (E). Twin modeling was conducted on raw ordinal

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data using Mx, which can accommodate missing data, and differential resemblance by zygosity was compared [19]. Twin pairs with incomplete trait data were included in the analyses as they contributed information for estimation of liability thresholds. Given that prevalence rates of ER vary with age, estimated liability thresholds were adjusted according to age of the participant. The Mx model for thresholds included regression of threshold on observed age at screening, using the definition variable approach [19]. A total of 455 MZ and 808 DZ female twin pairs from the TwinsUK cohort were available for analysis using this approach. Male individuals were excluded due to low numbers, particularly of affected male twins.

Due to the predominant female gender of the TwinsUK cohort and the lower prevalence of ER in females, two well-characterized large mixed-sex cohorts of unrelated individuals were subsequently included. The common SNP heritability from the combined genome-wide SNP data of the three cohorts (including males and the other siblings and singletons from the TwinsUK cohort) was estimated using GREML analysis from the Genome-wide Complex Trait Analysis (GCTA) package [21–23]. GREML is an assumption free method that quantifies the percentage of phenotypic variance explained by genome-wide SNPs using estimates of identity-by-state (IBS) sharing of alleles between pairs of unrelated individuals. The common SNP heritability estimate is denoted by h^2_{SNP} [23]. As the three cohorts were not enriched for ER cases, no correction was made for ascertainment bias (that is the prevalences were assumed to be equal to the proportions of cases observed in the sample), but a back-transformation from liability to case-control scale was applied [24]. The genetic relationship matrix was calculated between all pairs of individuals from all three cohorts and the set of individuals with a genetic relationship <0.05 was extracted from the dataset by GCTA to minimise any confounding effects of relatedness. Genome-wide and ER data were available for a total of 4009 unrelated individuals from the three cohorts. Age, sex, cohort, and the first five principle components (determined by GCTA) were included as covariates in the model [21].

The narrow-sense and common SNP heritabilities were estimated for overall ER and for ER subtypes: notched or slurred; lateral, inferior, or inferolateral; and rapidly ascending or horizontal/descending ST-segment morphology. For the subtype analyses, ER cases without the specific ER subtype were excluded and only subjects without ER were considered as controls.

3. Results

3.1. Subject and electrocardiogram characteristics

ECG data for 3539 twins (mean age 52.3 ± 12.4 years; 95.1% female) from the TwinsUK cohort were available. The proportion of MZ twins was 40.9% (Supplementary Table 1). ER was present in 237 (6.7%) subjects. In the BRIGHT cohort (n = 1358; mean age 59.1 ± 12.1 years; 62.3% female) ER was present in 132 (9.7%) subjects and in the GRAPHIC cohort (n = 932; mean age 52.8 ± 4.4 years; 50.5% female) ER was present in 74 (7.9%) subjects. Presence of ER was associated with younger age, male gender, lower resting heart rates, longer QRS duration, shorter corrected QT intervals and more rightward QRS axis (Supplementary Table 2). Rapidly ascending ST-segment morphology ER was associated with younger age, male gender, shorter QRS duration and shorter corrected QT interval (Supplementary Table 3). ER was most commonly slurred type (47.9%), inferior territory (42.2%), with horizontal/descending ST-segment morphology (58.0%) (Supplementary Table 4).

3.2. Heritability estimation

The results of the classical twin modeling analyses from TwinsUK are shown in Tables 1 and 2. For inferior and inferolateral ER, heritability could not be estimated as there were no concordant affected MZ twins in the dataset (Table 1). Except for horizontal/descending ST-segment ER, concordances and twin correlations were higher in MZ than DZ twin pairs. Using the Akaike's Information Criterion (AIC), the full ACE model (where A: additive genetic effects; C: common environmental factors and E: unique environmental factors) provided the best fit for all ER variables (Table 2) [25]. The influence of age on the liability threshold in the model was significant for lateral ER and rapidly ascending ST-segment morphology. Liability thresholds in the models for these variables were therefore adjusted for age. The estimated heritabilities ranged from 0.00 to 0.47, but none were statistically significant (see a^2 column in Table 2). Compared with the full ACE model, the models including the unique environmental factor E alone provided a worse fit for the data in all variables, except notched ER. This meant that A and C could not be dropped simultaneously without significant worsening of fit (Table 2). Estimates for familial resemblance were obtained from the MZ twin correlations as the sum of the proportion of variance in disease liability explained by additive genetic and common environmental factors (A + C) (see A + C column in Table 2). Except for notched ER, the estimates for familial resemblance for the ER subtypes that could be estimated, were significant and ranged from 0.49 to 0.67. The results of the GREML estimates of common SNP heritability from unrelated individuals in TwinsUK, GRAPHIC, and BRIGHT are shown in Table 3. These ranged from 0.00 to 0.36, and none were statistically significant.

4. Discussion

This is the first report of ER and ER subtype heritability using twin studies and genotyping data. Our population included MZ and DZ twins from TwinsUK as well as unrelated individuals from three large UK cohorts (TwinsUK, GRAPHIC and BRIGHT). Concordances and twin correlations were higher in MZ than DZ female twin pairs pointing to a genetic contribution in ER and ER subtypes, except for horizontal/descending ST-segment ER. Significant familial resemblance was found for ER and ER subtypes, except for notched ER. Whether this was due to genetic or common environmental origin could not be distinguished statistically. Classical twin modeling and GREML estimates of common SNP heritability were modest and without statistical significance. Therefore, it seems that although ER shows some genetic predisposition, there is significant environmental influence. Our modest heritability estimates may explain why GWAS have been unable to

Table 1
Concordance data and twin correlations for 455 monozygotic (MZ) and 808 dizygotic (DZ) twin pairs for early repolarization (ER) and ER subtypes (from the TwinsUK cohort). The 95% confidence interval is given in brackets.

		MZ					DZ				
		C	D	Concordance		Twin correlation	C	D	Concordance		Twin correlation
		(A/A)	(A/NA)	C_P	C_C		(A/A)	(A/NA)	C_P	C_C	
All ER	ER	11	46	0.19	0.33	0.52 (0.30–0.70)*	9	78	0.10	0.19	0.34 (0.12–0.54)*
ER by type	Notched	2	26	0.07	0.13	0.31 (−0.10–0.64)	2	44	0.04	0.08	0.21 (−0.14–0.52)
	Slurred	9	27	0.25	0.40	0.67 (0.44–0.83)*	7	45	0.13	0.24	0.52 (0.27–0.71)*
ER by territory	Inferior	0	14	0.00	0.00	n.a.	2	38	0.05	0.10	n.a.
	Lateral	3	20	0.13	0.23	0.51 (0.16–0.77)*	1	25	0.04	0.07	0.27 (−0.22–0.66)
	Inferolateral	0	12	0.00	0.00	n.a.	5	15	0.25	0.4	n.a.
ER by ST-segment morphology	RA	6	23	0.21	0.33	0.62 (0.35–0.82)*	4	42	0.09	0.16	0.39 (0.09–0.63)*
	HD	3	23	0.12	0.21	0.45 (0.09–0.73)*	5	36	0.12	0.22	0.52 (0.24–0.73)*

* p-Value < 0.05; RA, rapidly ascending ST-segment; HD, horizontal/descending ST-segment; C (A/A), number of concordant affected twin pairs; D (A/NA), number of discordant twin pairs; C_P, Pairwise concordance = C/(C + D); C_C, Casewise concordance = 2C/(2C + D); $C_{NA/NA}$ = 398 pairs of MZ twins and 721 pairs of DZ twins; n.a. not applicable (no MZ cases concordant for the disease).

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Table 2
Variance components and 95% CI of the full ACE model, test for the influence of age on the liability threshold and the fit of the familial resemblance using Mx in 1263 twin pairs (from the TwinsUK cohort). Narrow-sense heritability is indicated by a^2. The 95% confidence interval is given in brackets.

	ER subtypes	a^2	c^2	e^2	Influence of age on threshold	A + C	p-Value test drop A + C
All ER	ER	0.36 [0 to 0.70]	0.16 [0 to 0.54]	0.48 [0.30 to 0.69]*	0.01 [−0.0005 to 0.01]	0.52 [0.31 to 0.70]*	<0.001
ER by type	Notched	0.19 [0 to 0.62]	0.11 [0 to 0.48]	0.69 [0.38 to 1.00]*	−0.008 [−0.01 to 0.0006]	0.31 [0 to 0.62]	0.16
	Slurred	0.31 [0 to 0.82]	0.36 [0 to 0.70]	0.33 [0.17 to 0.54]*	0.00 [−0.09 to 0.005]	0.67 [0.46 to 0.83]*	<0.001
ER by territory	Inferior	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	Lateral	0.47 [0 to 0.76]	0.04 [0 to 0.63]	0.49 [0.24 to 0.83]*	−0.01 [−0.02 to −0.003]*	0.51 [0.17 to 0.76]*	0.01
	Inferolateral	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
ER by ST-segment morphology	RA	0.46 [0 to 0.82]	0.16 [0 to 0.63]	0.38 [0.19 to 0.65]*	−0.02 [−0.02 to −0.008]*	0.62 [0.35 to 0.81]*	<0.001
	HD	0 [0 to 0.67]	0.49 [0 to 0.67]	0.51 [0.27 to 0.72]*	0.007 [−0.001 to 0.02]	0.49 [0.28 to 0.73]*	<0.001

* p-Value<0.05; ER, early repolarization; RA, rapidly ascending ST-segment; HD, horizontal/descending ST-segment; CI, confidence interval; n.a. not applicable (no MZ cases concordant for the disease); a^2 = proportion of variance in disease liability explained by additive genetic factors (i.e. heritability); c^2 = proportion of variance in disease liability explained by common environment; e^2 = proportion of variance in disease liability explained by unique environment; drop A + C = test of the E model (familial resemblance).

find statistically significant genetic associations for ER or ER subtypes, and suggest larger studies will be required [13].

4.1. Comparison with other studies

Thus far heritability studies have been conducted in family and community based cohorts [8,9]. Prior analysis of 505 Caucasian nuclear families from the GRAPHIC cohort estimated the narrow-sense heritability using variance component analyses adjusted for age and sex. The estimated overall heritability of ER was 0.49 ± 0.14 ($p = 2.7 * 10^{-4}$) with higher estimates calculated for inferior and notched ER (0.61 ± 0.18 and 0.81 ± 0.19 respectively). When ER was present in the parents' ECGs, a 2.5 fold increased risk of the offspring presenting with ER was reported [9]. Another community-based cohort showed that siblings of subjects with ER carry a two-fold increased risk of ER themselves, although this was no longer significant after adjustment for age and sex [8].

Our heritability estimates are lower and not statistically significant. The differences may partly reflect differences in the populations studied as our cohort included a larger proportion of middle-aged Caucasian women (from TwinsUK). Although our sample size was not much greater than other studies, our analyses used SNPs to estimate the genetic similarity between unrelated individuals and compare that to their trait similarity. Differences in methodology may therefore explain the differences in results from prior studies, particularly the GRAPHIC analysis which used only family based h^2 estimates, not h^2_{SNP} estimation. A (additive genetic factors) and C (common environmental factors) are confounded in family studies, so the reported h^2 heritability estimates may have included a C component. Our findings imply that ER heritability is substantially lower than previously described.

4.2. ST-segment morphology

In our population, the ER ST-segment morphologies were found in similar proportions. Higher concordances and twin correlations in MZ compared with DZ twin pairs pointed to a genetic contribution for ER with a rapidly ascending ST-segment, but not ER with horizontal/descending ST-segment. ER with a rapidly ascending ST-segment also demonstrated greater heritability than ER with horizontal/descending ST-segment. This was not statistically significant, but large 95% confidence intervals suggest that this might be attributed to lack of power rather than non-existent genetic effects.

Previous retrospective analysis of a community-based cohort also found greater heritability of the rapidly ascending ST-segment morphology [26]. As this pattern is more prevalent in young male athletes, heritability studies in a younger more active cohort may clarify this more accurately. This ER subtype is considered benign and therefore the heritable component of ER does not appear to be associated with adverse outcomes. This is supported by findings that ER with horizontal/descending ST-segment has been associated with older age, ECG signs of coronary artery disease, and longer QRS duration, suggesting a more acquired phenotype [3]. Those with horizontal/descending ST-segments in our population were also older with longer QRS duration.

Previous work has shown that first-degree relatives of autopsy negative SCD victims have increased prevalence of ER with both rapidly ascending and horizontal/descending ST-segment morphologies, when compared to matched nuclear families [27]. A recent study demonstrated higher prevalence of ER in survivors of unexplained cardiac arrest (UCA) who had first-degree relatives with the ER pattern [28]. It therefore remains possible that ER is heritable when seen in the context of SCD and UCA and that ER with rapidly ascending ST-segment may not be completely 'benign' in this setting.

We also found that lateral and rapidly ascending ER subtypes were influenced by age. These subtypes are consistent with the historical description of ER [5]. The horizontal/descending subtype would only be considered ER according to more recent definitions, first described by Haissaguerre et al. [2] All ER is not necessarily the same and may explain why age influences lateral and rapidly ascending ER but not other subtypes [29].

Interestingly a recent GWAS of ST-segment and T wave voltage has identified SNP associations that might be relevant to ER-associated ST-segment morphology, but cannot yet be extrapolated directly to ER

Table 3
Common SNP heritability of early repolarization (ER) and ER subtypes estimated with Genomic Restricted Maximum Likelihood (GREML) analysis using 4009 unrelated individuals (all cohorts). All calculations adjusted for age, sex, cohort, and the first five principle components.

	ER subtypes	h^2_{SNP} (95% CI)	p-Value
All ER	All	0.07 (−0.31–0.45)	0.72
ER by type	Notched	0.00 (−0.59–0.59)	1.00
	Slurred	0.14 (−0.33–0.62)	0.56
ER by territory	Inferior	0.30 (−0.35–0.94)	0.38
	Lateral	0.36 (−0.40–1.12)	0.36
	Inferolateral	0.00 (−1.18–1.18)	1.00
ER by ST-segment morphology	Rapidly ascending	0.31 (−0.46–1.08)	0.42
	Horizontal/descending	0.00 (−0.51–0.51)	1.00

h^2_{SNP}, GREML estimate of the common SNP heritability; CI, confidence interval.

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[30]. J-point elevation ≥0.1 mV is required as part of the definition of ER and the J-point was not included in the analysis. Heritability estimates of the inferior ST-segment voltage were however on the low side, in part supporting our data.

4.3. Definitions

Our definition of ER stayed as true as possible to those used in studies that have associated ER with SCD events in the general population and in survivors of IVF [1–4]. Although accurate measurement of the notched ER pattern is usually straightforward, when transition from the terminal QRS into the ST-segment is unclear J-point elevation may be more subjective and this poses a problem for identifying slurred ER [29]. Despite this the interobserver reliability in the TwinsUK cohort was high with 98% concordance as well as 96% concordance between GRAPHIC and BRIGHT, indicating that our measurements are reliable.

4.4. Limitations

GREML can be used to analyse quantitative traits in family members, as it enables estimation of the narrow-sense heritability using identity-by-descent sharing rather than identity-by-state information, that is more accurate than the heritability estimates from structural equation modeling in Mx [22,23,31]. Unfortunately, current versions of GREML cannot be used for narrow-sense heritability estimation using relatives for binary traits such as ER, because the liability correction that is applied requires unrelated individuals. Mx heritability estimates which were derived from female twins only, were not statistically significant due to the low disease prevalence resulting in low power to differentiate between additive genetic factors and common environment in classical twin estimates. We attempted to estimate the percentage of phenotypic variance explained by common SNPs using GREML. However, all common SNP heritability estimates were non-significant, implying that analysis of a binary trait with a low prevalence with GREML has insufficient power resulting in unreliable estimates of the common SNP heritability. In addition h^2_{SNP} does not capture the contribution of rare variants.

5. Conclusion

ER and ER subtypes are traits with a modest to high familial component, but our analyses could not determine whether these are genetic or shared environmental factors. It therefore appears that although ER may show some genetic predisposition, there is significant environmental influence. These modest heritability estimates may explain why GWAS have been unable to find significant genetic signals for ER. Furthermore, we observed no significant differences between heritability of the ST-segment morphology subtypes.

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Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.09.119.

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